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**APPLICATION NUMBER:** ***60/604,274***
**FILING DATE:** ***August 25, 2004***

**PRIORITY DOCUMENT**
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| Docket Number | 4-33554P2 |
|---|---|

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EV540156132 4S
Express Mail Label Number

August 25, 2004
Date of Deposit

15866 U.S.PTO 082504

22151 U.S. PTO 60/604274 082504

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

# PATENT COVER SHEET FOR PROVISIONAL APPLICATION

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

| INVENTOR(S) | | |
|---|---|---|
| Given Name (first and middle [if any]) | Family Name or Surname | Residence (City and either State or Foreign Country) |
| | | |

TITLE OF THE INVENTION (280 characters max)

DIRECT COMPRESSION FORMULATION AND PROCESS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Including Any Claims and Abstract) - 23 pages
- ☐ Drawings - sheets
- ☐ Other (specify):

METHOD OF PAYMENT

| | |
|---|---|
| The Commissioner is hereby authorized to charge filing fee and any additional fees required to Deposit Account Number: 19-0134 in the name of Novartis. | PROVISIONAL FILING FEE AMOUNT: $ 160 |

☐ U.S. Government agency and contract number: (if the invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.)

Respectfully submitted,

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Date: August 25, 2004

# DIRECT COMPRESSION FORMULATION AND PROCESS

## FIELD OF THE INVENTION

This invention relates to tablets formed by direct compression of a dipeptidylpeptidase IV (DPP-IV) inhibitor compound, a process for the preparation thereof, and to new tableting powders comprising DPP-IV inhibitor formulations capable of being directly compressed into tablets. The invention relates further to a process for preparing the tablets by blending the active ingredient and specific excipients into the new formulations and then directly compressing the formulations into the direct compression tablets.

## BACKGROUND OF THE INVENTION

The preferred DPP-IV inhibitor compounds to which this invention is primarily directed are described below:

Preferred DPP-IV inhibitors are described in the following patent applications; WO 02053548 especially compounds 1001 to 1293 and examples 1 to 124, WO 02067918 especially compounds 1000 to 1278 and 2001 to 2159, WO 02066627 especially the described examples, WO 02/068420 especially all the compounds specifically listed in the examples I to LXIII and the described corresponding analogues, even preferred compounds are 2(28), 2(88), 2(119), 2(136) described in the table reporting IC50, WO 02083128 such as in the claims 1 to 5 especially compounds described in examples 1 to 13 and the claims 6 to 10, US 2003096846 especially the specifically described compounds, WO 2004/037181 especially examples 1 to 33, WO 0168603 especially compounds of examples 1 to 109, EP1258480 especially compounds of examples 1 to 60, WO 0181337 especially examples 1 to 118, WO 02083109 especially examples 1A to 1D, WO 030003250 especially compounds of examples 1 to 166, most preferably 1 to 8, WO 03035067 especially the compounds described in the examples, WO 03/035057 especially the compounds described in the examples, US2003216450 especially examples 1 to 450, WO 99/46272 especially compounds of claims 12, 14, 15 and 17, WO 0197808 especially compounds of claim 2, WO 03002553 especially compounds of examples 1 to 33, WO 01/34594 especially the compounds described in the examples 1 to 4, WO 02051836 especially examples 1 to 712,

EP1245568 especially examples 1 to 7, EP1258476 especially examples 1 to 32, US 2003087950 especially the described examples, WO 02/076450 especially examples 1 to 128, WO 03000180 especially examples 1 to 162, WO 03000181 especially examples 1 to 66, WO 03004498 especially examples 1 to 33, WO 0302942 especially examples 1 to 68, US 6482844 especially the described examples, WO 0155105 especially the compounds listed in the examples 1 and 2, WO 0202560 especially examples 1 to 166, WO 03004496 especially examples 1 to 103, WO 03/024965 especially examples 1 to 54, WO 0303727 especially examples 1 to 209, WO 0368757 especially examples 1 to 88, WO 03074500 especially examples 1 to 72, examples 4.1 to 4.23, examples 5.1 to 5.10, examples 6.1 to 6.30, examples 7.1 to 7.23, examples 8.1 to 8.10, examples 9.1 to 9.30, WO 02038541 especially examples 1 to 53, WO 02062764 especially examples 1 to 293, preferably the compound of example 95 (2-{{3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2 dihydro-6-isoquinolinyl}oxy}acetamide hydrochloride), WO 02308090 especially examples 1-1 to 1-109, examples 2-1 to 2-9, example 3, examples 4-1 to 4-19, examples 5-1 to 5-39, examples 6-1 to 6-4, examples 7-1 to 7-10, examples 8-1 to 8-8, examples 7-1 to 7-7 of page 90, examples 8-1 to 8-59 of pages 91 to 95, examples 9-1 to 9-33, examples 10-1 to 10-20, US 2003225102 especially compounds 1 to 115, compounds of examples 1 to 121,preferably compounds a) to z), aa) to az), ba) to bz), ca) to cz) and da) to dk), WO 0214271 especially examples 1 to 320, US 2003096857, U.S. application Serial No. 09/788,173 filed February 16, 2001 (attorney file LA50) especially the described examples, WO99/38501 especially the described examples, W099/46272 especially the described examples and DE19616 486 A1 especally val-pyr, val-thiazolidide, isoleucyl-thiazolidide, isoleucyl-pyrrolidide, and fumar salts of isoleucyl-thiazolidide and isoleucyl-pyrrolidide.

Further preferred DPP-IV inhibitors include the specific examples disclosed in United States Patent Numbers 6124305 and US 6107317, International Patent Applications, Publication Numbers WO 9819998, WO 95153 09 and WO 9818763; such as 1[2- [(5 eyanopyridin-2-yl)aminoethylamino]acetyl-2-cyano-(S)-pyrrolidine and (2S)- l-[(2S)-2 arnino-3,3-dimethylbutanoyl]-2-pyrrolidinecarbonitrile.

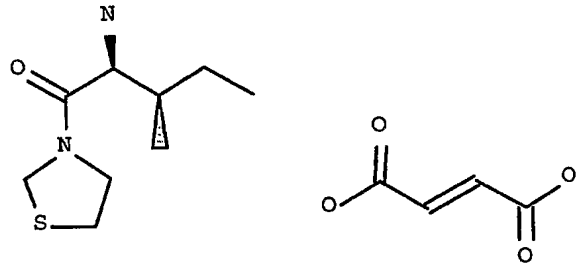
Preferred DPP-IV inhibitors are N-substituted adamantyl-amino-acetyl-2-cyano pyrrolidines, N (substituted glycyl)-4-cyano pyrrolidines, N- (N'-substituted glycyl)-2-cyanopyrrolidines, N-aminoacyl thiazolidines, N-aminoacyl pyrrolidines, L-allo-isoleucyl thiazolidine, L-threo-

isoleucyl pyrrolidine, and L-allo-isoleucyl pyrrolidine, 1-[2-[(5-cyanopyridin-2-yl) amino] ethylamino] acetyl-2-cyano-(S)-pyrrolidine and pharmaceutical salts thereof.

Preferred DPP-IV inhibitors are also those described by Mona Patel and col. (Expert Opinion Investig Drugs. 2003 Apr;12(4):623-33) on the paragraph 5, especially P32/98, K-364, FE-999011, BDPX, NVP-DDP-728 and others, which publication is hereby incorporated by reference especially the described DPP-IV inhibitors.

FE-999011 is described in the patent application WO 95/15309 page 14, as compound No. 18.

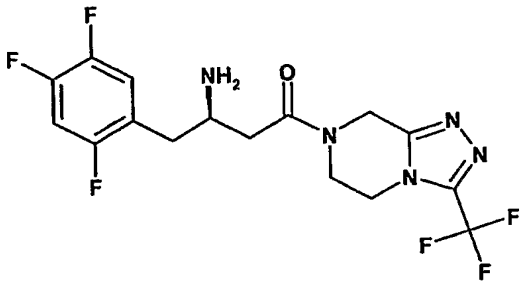
P32/98 or P3298 (CAS number: 251572-86-8) also known as 3-[(2S,3S)-2-amino-3-methyl-1-oxopentyl]thiazolidine can be used as 3-[(2S,3S)-2-amino-3-methyl-1-oxopentyl]thiazolidine and (2E)-2-butenedioate (2:1) mixture such as shown below



and is described in WO 99/61431 in the name of Probiodrug.

Other preferred DPP-IV inhibitors are described in the patent applications WO 2004/037169 especially those described in the examples 1 to 48 and WO 02/062764 especially the described examples 1 to 293, even preferred are the compounds 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide described on page 7 and also in the patent application WO2004/024184 especially in the reference examples 1 to 4.

Other preferred DPP-IV inhibitors are described in the patent application WO 03/004498 especially examples 1 to 33 and most preferably the compound of the formula



MK-0431

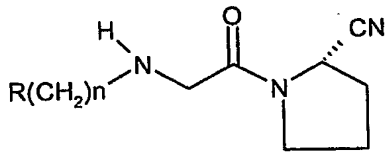
described by the example 7 and also known as MK-0431.

Preferred DPP-IV inhibitors are also described by Wallace T. Ashton (Bioorganic & Medicinal Chemistry Letters 14 (2004) 859-863 ) especially the compound 1 or the compound 21e (table 1) and the compounds listed in the tables 1 and 2.

Preferred DPP-IV inhibitors are also described in the patent application WO 2004/037181 especially examples 1 to 33 and most preferably the compounds described in the claims 3 to 5.

In each case in particular in the compound claims and the final products of the working examples, the subject matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications.

Most preferably the inhibitors are *N*-(substituted glycyl)-2-cyanopyrrolidines of formula (I)



**(I)**

wherein

R is substituted adamantyl; and

n is 0 to 3;

in free form or in acid addition salt form.

The term "substituted adamantly" refers to adamantyl, i.e., 1- or 2-adamantyl, substituted by one or more, e.g., two substituents selected from alkyl, $-OR_1$ or $-NR_2R_3$, where $R_1$, $R_2$ and $R_3$ are independently hydrogen, alkyl, ($C_1$-$C_8$alkanoyl), carbamyl, or $-CO-NR_4R_5$, where $R_4$ and $R_5$ are independently alkyl, unsubstituted or substituted aryl and where one of $R_4$ and $R_5$ additionally is hydrogen or $R_4$ and $R_5$ together represent $C_2$-$C_7$alkylene.

The term "aryl" preferably represents phenyl. Substituted phenyl preferably is phenyl substituted by one or more, e.g., two, substitutents selected from, e.g., alkyl, alkoxy, halogen and trifluoromethyl.

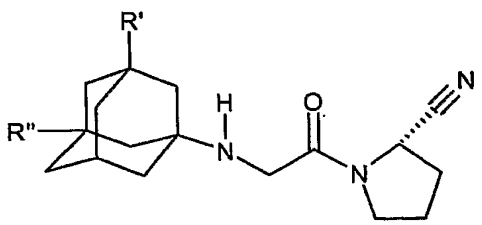
The term "alkoxy" refers to alkyl-O-.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "alkylene" refers to a straight chain bridge of 2 to 7 carbon atoms, preferably of 3 to 6 carbon atoms, most preferably 5 carbon atoms.

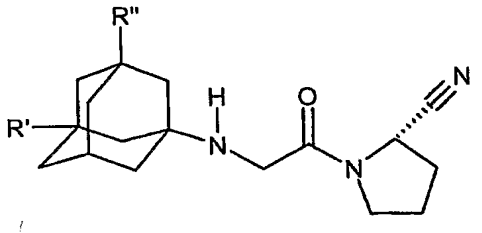
A preferred group of compounds of the invention is the compounds of formula (I), wherein the substituent on the adamantyl is bonded on a bridgehead or a methylene adjacent to a bridgehead. Compounds of formula (I), wherein the glycyl-2-cyanopyrrolidine moiety is bonded to a bridgehead, the R' substituent on the adamantyl is preferably 3-hydroxy. Compounds of formula (I), wherein the glycyl-2-cyanopyrrolidine moiety is bonded at a methylene adjacent to a bridgehead, the R' substituent on the adamantyl is preferably 5-hydroxy.

The present invention especially relates to a compound of formula (IA) or (IB)




**(IA)**

or




**(IB)**

wherein

R' represents hydroxy, $C_1$-$C_7$alkoxy, $C_1$-$C_8$alkanoyloxy or $R_5R_4N$-CO-O-, where $R_4$ and $R_5$ independently are $C_1$-$C_7$alkyl or phenyl which is unsubstituted or substituted by a substitutent selected from $C_1$-$C_7$alkyl, $C_1$-$C_7$alkoxy, halogen and trifluoromethyl and where $R_4$ additionally is hydrogen; or $R_4$ and $R_5$ together represent $C_3$-$C_6$alkylene; and

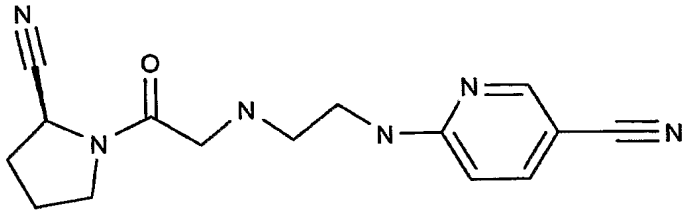
R" represents hydrogen; or

R' and R" independently represent $C_1$-$C_7$alkyl;

in free form or in form of a pharmaceutically acceptable acid addition salt.

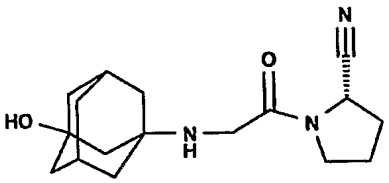
These DPP-IV inhibitor compounds of formula (I), (IA) or (IB) are known and described in U.S. Patent No. 6,166,063, issued December 26, 2000. They can exist in free form or in acid addition salt form. Pharmaceutically acceptable, i.e., non-toxic and physiologically acceptable, salts are preferred, although other salts are also useful, e.g., in isolating or purifying the compounds of this invention. Although the preferred acid addition salts are the hydrochlorides, salts of methanesulfonic, sulfuric, phosphoric, citric, lactic and acetic acid may also be utilized.

Especially preferred are 1-{2-[(5-cyanopyridin-2-yl) amino] ethylamino} acetyl-2-(S)-cyano-pyrrolidine, of formula :



especially the dihydrochloride or monohydrochloride form thereof,

(S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine (or pyrrolidine, 1-[(3-hydroxy-1-adamantyl) amino] acetyl-2-cyano-, (S) or LAF237) of formula



L-threo-isoleucyl thiazolidine (compound code according to Probiodrug: P32/98 as described above), MK-0431, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide and optionally pharmaceutical salts thereof.

[*S*]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride and (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine are specifically disclosed in Example 3 of WO 98/19998 and Example 1 of WO 00/34241, respectively. The DPP-IV inhibitor P32/98 (see above) is specifically described in Diabetes 1998, 47, 1253-1258. [*S*]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride and (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine can be formulated as described on page 20 of WO 98/19998 or in WO 00/34241.

The DPP-IV inhibitor compounds e.g. those of formula (I), and their corresponding pharmaceutically acceptable acid addition salts, may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, e.g., orally, in the form of tablets, capsules, caplets, etc. or parenterally, e.g., intravenously, in the form of sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

The DPP-IV inhibitor compounds e.g. those of formula (I), and their corresponding pharmaceutically acceptable acid addition salts, may be formulated into enteral and parenteral pharmaceutical compositions containing an amount of the active substance that is effective for treating conditions mediated by DPP-IV inhibition, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

The DPP-IV inhibitor compounds e.g. those of formula (I), including those of each of the sub-scopes thereof and each of the examples, may be administered in enantiomerically pure form, e.g., >98%, preferably >99%; or together with the R enantiomer, e.g., in racemic form. The above dosage ranges are based on the compounds of formula (I), excluding the amount of the R enantiomer.

In view of their ability to inhibit DPP-IV, the DPP-IV inhibitor compounds e.g. those of formula (I), and their corresponding pharmaceutically acceptable acid addition salts, are useful in treating conditions mediated by DPP-IV inhibition. Based on the above and findings in the literature, it is expected that the compounds disclosed herein are useful in the treatment of conditions, such as non-insulin-dependent diabetes mellitus, arthritis, obesity, allograft transplantation and calcitonin-osteoporosis. In addition, based on the roles of glucagon-like peptides, such as GLP-1 and GLP-2, and their association with DPP-IV inhibition, it is expected that the compounds disclosed herein are useful for example, to produce a sedative or anxiolytic effect, or to attenuate post-surgical catabolic changes and hormonal responses to stress, or to reduce mortality and morbidity after myocardial infarction, or in the treatment of conditions related to the above effects which may be mediated by GLP-1 and/or GLP-2 levels.

More specifically, e.g., the DPP-IV inhibitor compounds e.g. those of formula (I), and their corresponding pharmaceutically acceptable acid addition salts, improve early insulin response to an oral glucose challenge and, therefore, are useful in treating non-insulin-dependent diabetes mellitus.

The DPP-IV inhibitor compounds useful in this invention are hygroscopic, presents stability problems, and are not inherently compressible. Consequently, there is a need to provide a free-flowing and cohesive composition capable of being directly compressed into strong tablets with an acceptable *in vitro* dissolution profile. Tablets may be defined as solid dosage pharmaceutical forms containing drug substances with or without suitable fillers. They are produced by compression or compaction of a formulation containing the active ingredient and certain excipients selected to aid in the processing and to improve the properties of the product. Tablets may be coated or uncoated and are made from powdered, crystalline materials. They may include various diluents, binders, disintegrants, lubricants,

glidants and in many cases, colorants. Excipients used are classified according to the function they perform. For example, a glidant may be used to improve the flow of powder blend in the hopper and into the tablet die.

There has been widespread use of tablets since the latter part of the 19th century and the majority of pharmaceutical dosage forms are marketed as tablets. Major reasons of tablet popularity as a dosage form are simplicity, low cost and the speed of production. Other reasons include stability of drug product, convenience in packaging, shipping and dispensing. To the patient or consumer, tablets offer convenience of administration, ease of accurate dosage, compactness, portability, blandness of taste, ease of administration and elegant distinctive appearance.

Tablets may be plain, film or sugar coated bisected, embossed, layered or sustained-release. They can be made in a variety of sizes, shapes and colors. Tablets may be swallowed, chewed or dissolved in the buccal cavity or beneath the tongue. They may be dissolved in water for local or topical application. Sterile tablets are normally used for parenteral solutions and for implantation beneath the skin.

In addition to the active or therapeutic ingredients, tablets may contain a number of inert materials known as excipients. They may be classified according to the role they play in the final tablet. The primary composition includes a filler, binder, lubricant and glidant. Other excipients which give physical characteristics to the finished tablet are coloring agents, and flavors in the case of chewable tablets. Without excipients most drugs and pharmaceutical ingredients cannot be directly-compressed into tablets. This is primarily due to the poor flow and cohesive properties of most drugs. Typically, excipients are added to a formulation to impart good flow and compression characteristics to the material being compressed. Such properties are imparted to these excipients through pretreatment steps, such as wet granulation, slugging, spray drying spheronization or crystallization.

Lubricants are typically added to prevent the tableting materials from sticking to punches, minimize friction during tablet compression, and allow for removal of the compressed tablet from the die. Such lubricants are commonly included in the final tablet mix in amounts usually less than 1% by weight.

In addition, tablets often contain diluents which are added to increase the bulk weight of the blend resulting in a practical size for compression. This is often necessary where the dose of the drug is relatively small.

Another commonly used class of excipients in tablets is binders. Binders are agents, which impart cohesive qualities to the powdered material. Commonly used binders include starch, and sugars, such as sucrose, glucose, dextrose and lactose.

Disintegrants are often included to ensure that the tablet has an acceptable rate of disintegration. Typical disintegrants include starch derivatives and salts of carboxymethylcellulose.

Other desirable characteristics of excipients include the following:

- High-compressibility to allow strong tablets to be made at low compression forces;
- Good flow properties that can improve the flow of other excipients in the formula; and
- Cohesiveness (to prevent tablet from crumbling during processing, shipping and handling).

There are three commercially important processes for making compressed tablets: wet granulation, direct compression and dry granulation (slugging or roller compaction). The method of preparation and type of excipients are selected to give the tablet formulation the desired physical characteristics that allow for the rapid compression of the tablets. After compression, the tablets must have a number of additional attributes, such as appearance, hardness, disintegrating ability and an acceptable dissolution profile. Choice of fillers and other excipients will depend on the chemical and physical properties of the drug, behavior of the mixture during processing and the properties of the final tablets. Preformulation studies are done to determine the chemical and physical compatibility of the active component with proposed excipients.

The properties of the drug, its dosage forms and the economics of the operation will determine selection of the best process for tableting. Generally, both wet granulation and direct compression are used in developing a tablet.

The dry granulation method may be used where one of the constituents, either the drug or the diluent, has sufficient cohesive properties to be tabletted. The method consists of blending, slugging the ingredients, dry screening, lubrication and compression.

The wet granulation method is used to convert a powder mixture into granules having suitable flow and cohesive properties for tableting. The procedure consists of mixing the powders in a suitable blender followed by adding the granulating solution under shear to the mixed powders to obtain a granulation. The damp mass is then screened through a suitable screen and dried by tray drying or fluidized bed drying. Alternately, the wet mass may be dried and passed through a mill. The overall process includes weighing, dry powder blending, wet granulating, drying, milling, blending lubrication and compression.

In general, powders do not have sufficient adhesive or cohesive properties to form hard, strong granules. A binder is usually required to bond the powder particles together due to the poor cohesive properties of most powders. Heat and moisture sensitive drugs cannot usually be manufactured using wet granulation. The large number of processing steps and processing time are problems due to high level manufacturing costs. Wet granulation has also been known to reduce the compressibility of some pharmaceutical excipients, such as microcrystalline cellulose.

Direct compression is regarded as a relatively quick process where the powdered materials are compressed directly without changing the physical and chemical properties of the drug. The active ingredient(s), direct compression excipients and other auxiliary substances, such as a glidant and lubricant are blended in a twin shell blender or similar low shear apparatus before being compressed into tablets. This type of mixing was believed to be essential in order to prepare "pharmaceutically acceptable" dosage forms. Some pharmaceutical scientists believe that the manner in which a lubricant is added to a formulation must be carefully controlled. Accordingly, lubricants are usually added to a granulation by gentle mixing. It is also believed that prolonged blending of a lubricant with a granulation can materially affect hardness and disintegration time for the resulting tablets. Excessive blending of lubricants with the granulate ingredients can cause water proofing of the granule and reduces tablet hardness or strength of the compressed tablet. For these

reasons, high-shear mixing conditions have not been used to prepare direct compression dosage forms.

The advantages of direct compression include uniformity of blend, few manufacturing steps involved, i.e., the overall process involves weighing of powders, blending and compression, hence less cost; elimination of heat and moisture, prime particle dissociation and physical stability.

Pharmaceutical manufacturers would prefer to use direct compression techniques over wet or dry granulation methods because of quick processing time and cost advantages. However, direct compression is usually limited to those situations where the drug or active ingredient has a crystalline structure and physical characteristics required to form pharmaceutically acceptable tablets. However, one or more excipients must often be combined with the active ingredient before the direct-compression method can be used since many ingredients do not have the necessary properties. Since each excipient added to the formulation increases the tablet size of the final product, manufacturers are often limited to using the direct-compression method in formulations containing a low dose of the active ingredient per compressed tablet.

A solid dosage form containing a high-dose drug, i.e., the drug itself comprises a substantial portion of the total compressed tablet weight, could only be directly compressed if the drug itself has sufficient physical characteristics, e.g., cohesiveness, for the ingredients to be directly compressed.

For an example, the DPP-IV inhibitor e.g. those of formula (I) is considered a high-dose drug. Most tablet formulations include a range of 70-85% by weight of DPP-IV inhibitor per tablet. This high-dose drug, combined with its rather poor physical characteristics for direct compression, has not permitted direct compression as a method to prepare the final tablet. In addition, the active ingredients have poor stability in presence of water, another factor militating against the use of the wet granulation method.

Another limitation of direct compression as a method of tablet manufacturing is the potential size of the compressed tablets. If the amount of active ingredient is high, a pharmaceutical formulator may choose to wet granulate the active ingredient with other

excipients to attain an acceptable sized tablet with the desired amount of active ingredient. The amount of filler, binder or other excipients needed in wet granulation is less than that required for direct compression since the process of wet granulation contributes toward the desired physical properties of the tablet.

Hydroxypropyl methylcellulose has been utilized in the pharmaceutical industry as a direct compression excipient for solid dose forms. Hydroxypropyl methylcellulose is a processed cellulose and controls drug release from solid dosage forms.

Despite the advantages of the direct compression, such as reduced processing time and cost, wet granulation is widely-used in the industry to prepare solid dosage forms. Wet granulation is often preferred over direct compression because wet granulation has a greater chance of overcoming any problems associated with the physical characteristics of various ingredients in the formulation. This provides material which has the required flow and cohesive properties necessary to obtain an acceptable solid dosage form.

The popularity of wet granulation compared to direct compression is based on at least three advantages. First, wet granulation provides the material to be compressed with better wetting properties, particularly in the case of hydrophobic drug substances. The addition of hydrophilic excipients makes the surface of the hydrophobic drug more hydrophilic, reducing disintegration and dissolution problems. Second, the content uniformity of the solid dosage form is generally improved with wet granulation because all of the granules usually contain the same amount of drug. Lastly, the segregation of drug(s) from excipients is avoided.

Segregation could be a potential problem with direct compression. The size and shape of particles comprising the granulate to be compressed are optimized through the wet granulation process. This is because when a dry solid is wet granulated the binder "glues" particles together, so that they agglomerate into spherical granules.

In spite of the advantages afforded by wet granulation in general, due to the instability of the compounds in the presence of water, it is desirable to directly compress tablets containing high-dose DPP-IV inhibitor, e.g. as that defined in formula (I). There is a

need in the industry for techniques and pharmaceutical excipients which will allow manufacturers to prepare high-dose DPP-IV inhibitor tablets by direct compression.

## OBJECTS OF THE INVENTION

It is an object of the invention to provide a DPP-IV inhibitor formulation in the form of a free-flowing, cohesive tableting powder, capable of being directly compressed into a tablet.

It is a further object of the invention to provide a compressed DPP-IV inhibitor tablet in unit dosage form having an acceptable dissolution profile, as well as acceptable degrees of hardness and resistance to chipping, as well as a short disintegration time.

It is a further object of the invention to provide a process for preparing a compressed DPP-IV inhibitor tablet by direct compression in unit dosage form.

## SUMMARY OF THE INVENTION

The present invention provides a direct tableting, free-flowing particulate DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet having adequate hardness, rapid disintegration time and an acceptable dissolution pattern.

In addition to the active ingredient, the tableting powder contains a number of inert materials known as excipients. They may be classified according to the role they play in the final tablet. The primary composition includes fillers, binders or diluents, lubricants, disintegrants and glidants. Other excipients which give physical characteristics to the finished tablet are coloring agents, and flavors in the case of chewable tablets. Typically, excipients are added to a formulation to impart good flow and compression characteristics to the material being compressed.

The preferred formulation of this invention comprises the following: the active ingredient which is the DPP-IV inhibitor compound, the binders or diluents which are microcrystalline cellulose and lactose, the disintegrant which is sodium starch glycolate and the lubricant which is magnesium stearate.

The preferred diluents include microcrystalline cellulose which is manufactured by the controlled hydrolysis of alpha-cellulose, obtained as a pulp from fibrous plant materials, with dilute mineral acid solutions. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray dried to form dry, porous particles of a broad size distribution. Suitable microcrystalline cellulose will have an average particle size of from about 20 nm to about 200 nm. Microcrystalline cellulose is available from several suppliers. Suitable microcrystalline cellulose includes Avicel PH 101, Avicel PH 102, Avicel PH 103, Avicel PH 105 and Avicel PH 200, manufactured by FMC Corporation. Particularly preferred in the practice of this invention is Avicel PH 102, which has the smallest surface area and pore structure. Preferably the microcrystalline cellulose is present in a tablet formulation in an amount of from about 25% to about 70% by weight. Another preferred range of this material is from about 30% to about 35% by weight; yet another preferred range of from about 30% to about 32% by weight.

Another diluent is lactose. Preferably, the lactose is ground to have an average particle size of between about 50 μm and about 500 μm prior to formulating. The lactose is present in the tablet formulation in an amount of from about 5% to about 40% by weight, and can be from about 18% to about 35% by weight, and most preferred, can be from about 20% to about 25% by weight.

A disintegrant is also an optional but useful component of the tablet formulation. Disintegrants are included to ensure that the tablet has an acceptable rate of disintegration. Typical disintegrants include starch derivatives and salts of carboxymethylcellulose. Sodium starch glycolate is the preferred disintegrant for this formulation. Preferably the disintegrant is present in the tablet formulation in an amount of from about 0% to about 10% by weight, and can be from about 1% to about 4% by weight, and most preferred, can be from about 1.5% to about 2.5% by weight.

Lubricants are typically added to prevent the tableting materials from sticking to punches, minimize friction during tablet compression and allow for removal of the compressed tablet from the die. Such lubricants are commonly included in the final tablet mix in amounts usually less than 1% by weight. The lubricant component may be hydrophobic or hydrophilic. Examples of such lubricants include stearic acid, talc and

magnesium stearate. Magnesium stearate reduces the friction between the die wall and tablet mix during the compression and ejection of the tablets. It helps prevent adhesion of tablets to the punches and dies. Magnesium stearate also aids in the flow of the powder in the hopper and into the die. It has a particle size range of 450-550 microns and a density range of 1.00-1.80 g/mL. It is stable and does not polymerize within the tableting mix. The preferred lubricant, magnesium stearate is also employed in the formulation. Preferably, the lubricant is present in the tablet formulation in an amount of from about 0.25% to about 6%; also preferred is a level of about 0.5% to about 4% by weight; and most preferably from about 0.1% to about 2% by weight. Other possible lubricants include talc, polyethylene glycol, silica and hardened vegetable oils. In an optional embodiment of the invention, the lubricant is not present in the formulation, but is sprayed onto the dies or the punches rather than being added directly to the formulation.

Other conventional solid fillers or carriers, such as, cornstarch, calcium phosphate, calcium sulfate, calcium stearate, magnesium stearate, stearic acid, glyceryl mono- and distearate, sorbitol, mannitol, gelatin, natural or synthetic gums, such as carboxymethyl cellulose, methyl cellulose, alginate, dextran, acacia gum, karaya gum, locust bean gum, tragacanth and the like, diluents, binders, lubricants, disintegrators, coloring and flavoring agents could optionally be employed.

The particular components in the preferred formulation are the following:

(a) 30-32% by weight on a dry weight basis of DPP-IV inhibitor e.g. DPP-IV inhibitor of formula (I);

(b) 40-45% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 20-25% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 1.5-2% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) 0.1-2% by weight on a dry weight basis of magnesium stearate.

Another preferred formulation is the following:

(a) 30-35% by weight on a dry weight basis of DPP-IV inhibitor e.g. DPP-IV inhibitor of formula (I);

(b) 35-50% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 18-35% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 1-4% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) 0.5-4% by weight on a dry weight basis of magnesium stearate.

Still another preferred formulation is the following:

(a) 25-35% by weight on a dry weight basis of DPP-IV inhibitor e.g. DPP-IV inhibitor of formula (I);

(b) 25-70% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) 5-40% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) 0-10% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate;

(e) 0.25-6% by weight on a dry weight basis of magnesium stearate.

The invention also provides a process for preparing a compressed DPP-IV inhibitor tablet in unit dosage form which comprises:

(a) blending as a % by weight on a dry weight basis:

(i) 30-32% by weight on a dry weight basis of DPP-IV inhibitor e.g. DPP-IV inhibitor of formula (I);

(ii) 40-45% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose (Avicel PH 102);

(iii) 20-25% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(iv) 1.5-2% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(v) 0.1-2% by weight on a dry weight basis of magnesium stearate,

to form a DPP-IV inhibitor formulation in the form of a tableting powder, capable of being directly compressed into a tablet; and

(b) compressing the formulation prepared during step (a) to form the compressed DPP-IV inhibitor tablet in unit dosage form.

This present invention of direct compression of DPP-IV inhibitor involves blending and compression. The choice of grades of excipients took into consideration particle size maintained within a range that allows homogeneity of the powder mix and content uniformity of DPP-IV inhibitor. It prevents segregation of powders in the hopper during direct compression. The advantages of using these excipients are that they impart compressibility, cohesiveness and flowability of the powder blend. In addition, the use of direct compression provides competitive unit production cost, eliminates heat and moisture, allows for prime particle dissociation, physical stability and ensures particle size uniformity.

The final product is prepared in the form of tablets, capsules or the like by employing conventional tableting or similar machinery.

This invention is further illustrated by the following example:

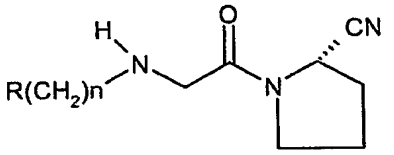
**Example 1**

To prepare the 25 mg tablet size, a batch size of 7 kg is prepared using amounts corresponding to the following per unit: 25 mg per unit of the compound 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile is mixed with 35.1 mg of microcrystalline cellulose, 17.5 mg anhydrous lactose and 1.6 mg sodium starch glycolate. The ingredients are pre-blended together in a commercial bin blender, then sieved through a 500 µm or 850 µm screen. The mix is blended again in the bin blender, then the necessary amount of the magnesium stearate to yield the 0.8 mg magnesium stearate per 25 mg tablet size, is added. Blending in each step is conducted at about 150-450 rotations, to ensure homogeneity of the mixture. Following blending again in the bin blender, the mix can be tabletted in a conventional tableting machine. The individual tablet weight for the 25 mg tablet is 80 mg. Tablets having 50 mg active ingredient weigh 160 mg, and 100 mg active ingredient tablets weigh 320 mg, respectively. The blend is a powder which has excellent compressibility into the desired tablet size.

What is claimed is:

1. A composition comprising the following:

(a) 25-35% by weight on a dry weight basis of a DPP-IV inhibitor especially an *N*-(substituted glycyl)-2-cyanopyrrolidine having the following formula (I)




**(I)**

wherein

R is substituted adamantyl; and

n is 0 to 3;

in free form or in acid addition salt form.

(b) from about 25% to about 70% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose such as Avicel PH 102;

(c) from about 5% to about 40% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) from about 0% to about 10% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) from about 0.25% to about 6% by weight on a dry weight basis of a pharmaceutically acceptable magnesium stearate.

2. The composition of Claim 1 in which the DPP-IV inhibitor is selected from [*S*]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride, 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile, L-threo-isoleucyl thiazolidine, MK-0431, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide, and optionally pharmaceutical salts thereof.

3. The composition of Claim 1 in which the *N*-(substituted glycyl)-2-cyanopyrrolidine is 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile.

4. The composition of Claim 1, wherein the components are the following:

(a) from about 30% to about 35% by weight on a dry weight basis of DPP-IV inhibitor or a DPP-IV inhibitor a of formula (I);

(b) from about 35% to about 50% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) from about 18% to about 35% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) from about 1% to about 4% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate;

(e) from about 0.5% to about 4% by weight on a dry weight basis of magnesium stearate.

5. The composition of Claim 4 in which the DPP-IV inhibitor is selected from [*S*]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride, 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile, L-threo-isoleucyl thiazolidine, MK-0431, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide, and optionally pharmaceutical salts thereof.

6. The composition of Claim 4, in which the *N*-(substituted glycyl)-2-cyanopyrrolidine is 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile.

7. The composition of Claim 1, wherein the components are the following:

(a) from about 30% to about 32% by weight on a dry weight basis of a DPP-IV inhibitor or a DPP-IV inhibitor of formula (I);

(b) from about 40% to about 45% by weight on a dry weight basis of a pharmaceutically acceptable microcrystalline cellulose;

(c) from about 20% to about 25% by weight on a dry weight basis of a pharmaceutically acceptable lactose;

(d) from about 1.5% to about 2.5% by weight on a dry weight basis of a pharmaceutically acceptable sodium starch glycolate; and

(e) from about 0.1% to about 2% by weight on a dry weight basis of magnesium stearate.

8. The composition of Claim 7 in which the DPP-IV inhibitor is selected from [*S*]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride, 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile, L-threo-isoleucyl thiazolidine, MK-0431, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide, and optionally pharmaceutical salts thereof.

9. The composition of Claim 7, in which the *N*-(substituted glycyl)-2-cyanopyrrolidine is 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile.

10. A solid dosage form of the composition of Claim 1.

11. The solid dosage form of Claim 10 which is a tablet.

12. The solid dosage form of Claim 10 which is a capsule.

13. The composition of Claim 10, in which the *N*-(substituted glycyl)-2-cyanopyrrolidine is 1-[3-hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(*S*)-carbonitrile.

## ABSTRACT OF THE INVENTION

Dipeptidylpeptidase IV inhibitor (herein referred to as DPP-IV) that may be 98.5-100% pure is a high-dose drug capable of being directly compressed with specific excipients into sold form dosage forms, such as tablets and capsules having desired, hardness, disintegrating ability and acceptable dissolution characteristics. DPP-IV is not inherently compressible and thus presents formulation problems. Excipients used in the formulation enhance the flow and compaction properties of the drug and tableting mix. Optimal flow contributes to uniform die fill and weight control. The binder used ensures sufficient cohesive properties that allow DPP-IV to be compressed using the direct compression method. The tablets produced provide an acceptable *in vitro* dissolution profile.